

nicotine, including current and passive smokers and those on nicotine replacement treatment, may have increased in situ CYP2D-mediated metabolism of centrally acting drugs and toxins as well as altered endogenous neurochemical metabolism owing to the higher CYP2D protein levels in brain. In addition, these individuals may be at altered risk for neurotoxin-mediated neurodegenerative diseases, such as Parkinson's disease.

### PT-14

**SULFONYLUREA DRUGS LIMIT COMPENSATORY  $K_{ATP}$  CHANNEL OPENING IN LONG QT SYNDROME.** S. Sattiraju, MD, L. V. Zingman, MD, S. Reyes, BS, A. E. Alekseev, PhD, A. Terzic, MD, PhD, Mayo Clinic, Rochester, MN.

**BACKGROUND:** Congenital or drug-induced long QT syndrome (LQTS) is characterized by QT interval prolongation on the electrocardiogram and the occurrence of life-threatening arrhythmias or sudden death, especially under conditions of stress. Prolongation of cardiac repolarization results in increased energy consumption to maintain cellular homeostasis. Cardiac  $K_{ATP}$  channels are membrane-based metabolic sensors that are able to adjust action potential duration (APD) under conditions of increased energy demand. Here we tested the role of normal  $K_{ATP}$  channel function in the development of LQTS, and the outcome of channel blockade by oral-hypoglycemic sulfonylurea drugs on pro-arrhythmic action potential prolongation.

**METHODS:** Retrogradely perfused hearts were paced in the physiological range. APD was evaluated using monophasic action potential (MAP) recording. The contribution of  $K_{ATP}$  channel-dependent APD modulation was validated in wild-type (WT) and  $K_{ATP}$  channel-deficient (Kir6.2-KO) transgenic models at different heart rates, in the presence and absence of the sulfonylurea glyburide. LQTS was produced by non-specific potassium channel blockade with 4-aminopyridine (4-AP) or blockade of sodium channel inactivation with anthopleurin-A. *In vivo* ECG telemetry recording was used to assess arrhythmogenic effects.

**RESULTS:** Increase in heart rate caused APD shortening. This shortening had a significant  $K_{ATP}$  channel component at high heart rates and was diminished by glyburide. This glyburide-sensitive component was also identified under drug-induced APD prolongation in WT but not in Kir6.2-KO at higher but not slower heart rates indicating an energetic load-dependent control of APD by  $K_{ATP}$  channels. *In vivo* ECG telemetry in the absence of functional  $K_{ATP}$  channels revealed significantly higher vulnerability to drug-induced development of QT prolongation and polymorphic ventricular tachycardia (TdP).

**CONCLUSION:**  $K_{ATP}$  channels are critical in limiting drug-induced APD prolongation especially at high cardiac workload. This cardioprotective effect is counteracted by sulfonylureas. This study identifies  $K_{ATP}$  channels as potential therapeutic targets for the treatment of LQTS, and points to potentially harmful electrophysiological effects of sulfonylurea drugs.

### OI-A-I

**POPULATION PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) MODEL OF THE VASCULAR-DISRUPTING AGENT 5,6-DIMETHYLXANTHENE-4-ACETIC ACID (DMXAA) IN CANCER PATIENTS.** J. Li, PhD, M. B. Jameson, MD, B. C. Baguley, MD, R. Pili, MD, S. D. Baker, PharmD, PhD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Waikato Hospital, University of Auckland, Baltimore, MD.

**BACKGROUND:** DMXAA selectively disrupts established tumor blood vessels. The degree of DMXAA-induced tumor hemorrhagic necrosis is correlated with increased plasma 5-hydroxyindole-3-acetic acid (5-HIAA) (a metabolite of serotonin). DMXAA is being evaluated in phase II trials in combination with cytotoxics.

**METHODS:** The plasma DMXAA and 5-HIAA concentration data were obtained from 124 patients receiving DMXAA monotherapy as 20-min intravenous infusion weekly or every three weeks at doses ranging from 6 to 4900 mg/m<sup>2</sup> in three phase I trials. The PK

and PD data were analyzed by nonlinear mixed effect modeling with NONMEM program. Potential covariates including age, body weight, height, body surface area (BSA), sex, liver and kidney functions were screened with general additive model analysis and tested in the PK/PD model.

**RESULTS:** DMXAA concentration-time profiles were well described by a 3-compartment model with saturable elimination (Michaelis-Menten kinetic). BSA and sex were significant covariates on the volume of distribution of the central compartment (V1) and the maximum elimination rate (VM), respectively, accounting for 10 and 12% of interindividual variation in these parameters. Population estimates for VM, KM (concentration at which half VM is achieved), and V1 were  $122 \times (1 + 0.502 \times (2-SEX))$  ( $\mu\text{M/h}$ ) [SEX = 1 for males, 2 for females], 103  $\mu\text{M}$ , and  $8.15 \times (BSA/1.8)^{0.69}$  (L), respectively. Plasma DMXAA and 5-HIAA concentrations were simultaneously fitted by the effect compartment PK-PD model with population PK parameters fixed to the previously obtained values from the final PK model. The effect of DMXAA on plasma 5-HIAA was described by the stimulatory  $E_{\text{max}}$  model, where population estimates for baseline,  $E_{\text{max}}$ , and  $EC_{50}$  were 46.2  $\mu\text{M}$ , 2.75-fold increase of the baseline value, and 659  $\mu\text{M}$ , respectively.

**CONCLUSIONS:** DMXAA plasma disposition is characterized by a saturable elimination process. BSA-guided dosing is important. 5-HIAA can be used as a biomarker to guide dose selection. DMXAA doses of 1000 to 2000 mg/m<sup>2</sup>, resulting in 1.5- to 1.8-fold increase of plasma 5-HIAA, are recommended for phase II/III studies.

### OI-A-II

**THE DOSE-RESPONSE RELATIONSHIP BETWEEN MANNITOL AND INTRACRANIAL PRESSURE IN TRAUMATIC BRAIN INJURY PATIENTS.** M. D. Sorani, UCSF, San Francisco, CA.

**BACKGROUND/AIMS:** Brain edema, an increase in water content in the brain, plays an important role in the pathophysiology of traumatic brain injury (TBI). Edema can increase intracranial pressure (ICP) and lead to ischemia and death. Brain edema is often treated with intravenous hyperosmotic agents to draw water out of tissue and decrease ICP. Mannitol, an alcohol sugar, is the osmotic diuretic most commonly used, yet no definitive dose-response relationship has been established. The specific relationship is important since high doses increase serum osmolality and have been associated with renal failure, whereas low doses may be ineffectual. Our aim was to characterize the dose-response relationship between mannitol and ICP in TBI patients.

**METHODS:** In a retrospective study at an urban trauma center intensive care unit, we measured ICP using a continuous physiological monitoring system in 28 consecutive TBI patients who were given at least one bolus of mannitol. Twenty patients were given a total of 85 doses of 50 g of mannitol, and 18 patients were given 50 doses of 100 g. Some patients received both doses.

**RESULTS:** Average ICP was  $22.0 \pm 10.6$  mm Hg at the time mannitol was administered, fell immediately after dosing, and continued falling for approximately 30 minutes to  $15.7 \pm 8.1$  mm Hg across all patients. After 30 minutes, ICP in the 100 g group ( $15.6 \pm 10.9$  mm Hg) was similar to that in the 50 g group ( $15.7 \pm 6.3$  mm Hg). However at 100 minutes, ICP had increased in the 50 g group to nearly its initial value but was lower in the 100 g group ( $18.6 \pm 7.6$  v.  $14.2 \pm 6.7$  mm Hg;  $p = .001$ ). We plotted ICP decrease versus weight-adjusted dose and found a linear relationship ( $y = 12.1x - 5.6$ ,  $p = .003$ ). The relationship indicates that each additional 0.1 g/kg mannitol achieves an additional reduction of approximately 1.2 mm Hg in ICP. When we separately analyzed doses given when patient ICP was greater than or less than 20 mm Hg, we found that doses given when ICP was high resulted in 36% or 43% decreases in ICP respectively for doses of 50 g or 100 g, while doses given when ICP was low showed only 4% or 13% decreases in ICP respectively.

**CONCLUSION:** In the first large study of continuous ICP dose-response data, we found that there is a linear relationship between mannitol dose and ICP response and that mannitol does not appreciably reduce ICP when it is not elevated.

### OI-A-III

A PHARMACODYNAMIC MODEL FOR THE TIME COURSE OF TUMOR SHRINKAGE ASSOCIATED WITH GEMCITABINE CHEMOTHERAPY IN ASIAN NON-SMALL CELL LUNG CANCER PATIENTS. L. Tham, MSc, PharmD, L. Wang, MSc, R. A. Soo, MD, S. Lee, MD, H. Lee, PhD, W. Yong, MD, B. Goh, MD, N. H. Holford, MB, ChB, National University Hospital, National University of Singapore, University of Auckland, Singapore.

**BACKGROUND/AIMS:** This study hypothesized that a longitudinal exposure-response model that describes and predicts anticancer effect of an oncology agent on tumor growth can be established from primary lesion(s) shrinkage in non-small cell lung cancer following gemcitabine chemotherapy. This pharmacodynamic model aims to describe tumor response over time and determine if quantitative exposure metrics for gemcitabine, or that of its metabolites, dFdU or dFdCTP were better than drug doses.

**METHODS:** Gemcitabine was given as an intravenous infusion on days 1 and 8 every 3 weekly in combination with carboplatin, administered only on day 1 of each cycle. Carboplatin dosing was fixed at a targeted area under concentration-time-curve (AUC) of 5 min-mg/ml. Doses and areas under the concentration-time curve (AUCs) of plasma gemcitabine, dFdU and intracellular, dFdCTP in white cells, were compared to determine which best describes primary tumor shrinkage over time. Pharmacokinetic and pharmacodynamic parameters were estimated using NONMEM (version V, release 1.1).

**RESULTS:** Tumor response over an average follow-up period 133 days was better described by a gemcitabine dose-driven Emax, rather than a sigmoid Emax model. The pharmacodynamic parameters derived using a Gompertz model for tumor growth kinetics were 6.61 cm for baseline tumor size ( $Size_0$ ), 1670 h for tumor turnover half-life, 8547.5 mg for gemcitabine dose ( $Dose_{50}$ ) at 50% tumor shrinkage, 450 h for effect transit half-life, and 950 h for tumor shrinkage factor (a hypothetical effect mediator) half-life. Between subject variability for  $Size_0$  and  $Dose_{50}$  were 75% and 112% respectively. Mean dose administered for this study was 15% of  $Dose_{50}$ .

**CONCLUSION:** The results of this study did not show that intracellular dFdCTP concentrations in white cells were good surrogates for dFdCTP concentrations or anti-tumor activity, in tumor cells. However, tumor shrinkage of the primary lesion(s) was successfully quantified using gemcitabine doses. This shows that exposure-response models in solid tumors can add valuable information to the decision-making process in drug development by utilizing tumor size measurements conducted during early phase clinical trials to quantify and predict anti-tumor effects.

### OI-A-IV

POPULATION PHARMACOKINETIC AND PHARMACODYNAMIC MODELING OF MYDRIASIS AFTER ADMINISTRATION OF ATOMOXETINE, DULOXETINE, AND REBOXETINE AS A POTENTIAL BIOMARKER FOR NOREPINEPHRINE REUPTAKE INHIBITOR. W. Byon, MS, D. Beidler, R. Duan, D. Roman, S. Chapel, M. Huttmacher, K. G. Kowalski, P. Lockwood, University of Minnesota, Pfizer Global Research and Development, Minneapolis, MN.

**BACKGROUND/AIMS:** Norepinephrine (NE) and serotonin have been implicated in fibromyalgia pain via their dysfunction at the descending inhibitory pain pathway (DIPP) in the brain and spinal cord. PKPD data was collected and analyzed from a study designed to determine the potential for mydriasis as a type 1 biomarker for new therapeutic agents that target the NE component of this DIPP mechanism.

**METHODS:** The mydriatic effect of atomoxetine (40 mg) [A], duloxetine (80 mg) [D], S,S-reboxetine (6 mg) [R], and placebo was determined in a single-dose randomized crossover study in 16 subjects with a 7-day washout period separating treatments. Plasma samples and pupil diameter were measured over 48 hours for each treatment. PKPD modeling was performed using NONMEM to characterize the time course of mydriasis. Posterior predictive checks evaluated the compatibility of the data and model. The potency relative to duloxetine was determined based on EC50 estimates and protein binding data and compared with in vitro binding studies.

**RESULTS:** All drugs were described by a one-compartment model with first order absorption and elimination. An effect compartment model characterized the delay between plasma concentrations and change in pupil diameter. The model included two fixed effects for the baseline ( $E_0$ ) score to reflect the study design. The change in the pupil diameter relative to effect site concentration was characterized by an Emax model with one Emax (95% CI) of 1.74 mm (1.22–2.26) for all drugs. The equilibration rate constants (95% CI, equilibration half-time) were  $0.031 \text{ hr}^{-1}$  (0.005–0.062, 22 hr) for A,  $0.657 \text{ hr}^{-1}$  (0.081–1.233, 1.1 hr) for D, and  $0.089 \text{ hr}^{-1}$  (0.039–0.138, 7.8 hr) for R. The relative potencies from the in vivo and in vitro methods are as follows:

Clinical Data	NE Receptor Binding Assay Data				
	EC50 <sub>total</sub> (95% CI) (ng/ml)	EC50 <sub>unbound</sub> (ng/ml)	Relative Potency (RP)	Ki (nm)	RP
Drug					
A	77.6 (0–199)	1.0	3.2	1.8	9.4
R	16.7 (3.55–29.9)	0.3	10.2	2	8.5
D	65.1 (15.7–115)	3.3	1.0	17	1.0

**CONCLUSIONS:** The study showed that mydriasis can be used as a type 1 biomarker for compounds with NE reuptake inhibition. Relative potency estimates from the study were consistent with estimates from preclinical binding assays except for atomoxetine which had poor precision. Based on the equilibration half-time and relative potency estimates, duloxetine was the fastest acting drug and reboxetine was the most potent drug.

### OI-B-I

GENETIC POLYMORPHISMS IN HUMAN ORGANIC CATION TRANSPORTER 1 (OCT1) ARE DETERMINANTS OF METFORMIN DISPOSITION AND RESPONSE. Y. Shu, MD, C. Brown, PharmD, R. P. Owen, PhD, S. Zhang, PhD, R. A. Castro, MD, E. T. Lin, PhD, J. Lo, MD, E. G. Burchard, MD, C. M. Brett, MD, K. M. Giacomini, PhD, University of California at San Francisco, San Francisco, CA.

**BACKGROUND/AIMS:** We and others previously demonstrated that human *SLC22A1* gene, which encodes organic cation transporter 1 (OCT1), is highly polymorphic in human populations. Metformin is a widely used anti-diabetic agent, and has been characterized as an OCT1 substrate. The goal of this study was to determine whether the genetic variants of OCT1 alter the disposition and response to metformin in cells and in humans.

**METHODS:** Stable HEK-293 cells expressing empty vector, OCT1-reference, and twelve OCT1 nonsynonymous variants were generated respectively. Metformin uptake was measured, and immunoblots were performed to examine the activation of AMPK and ACC by metformin in the stable cells. After informed consent was obtained, twenty healthy volunteers with different OCT1 genotypes were recruited into an open-label clinical study conducted in the General Clinical Research Center at San Francisco General Hospital. Metformin pharmacokinetics and plasma glucose concentrations from oral glucose tolerance tests (OGTT) were compared between volunteers who carried a decreased function OCT1 variant (variant volunteers,